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(54) **ERODIBLE MATRIX FOR SUSTAINED RELEASE BIOACTIVE COMPOSITION.**(30) Priority: **23.07.84 US 633604**(43) Date of publication of application:
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(73) Proprietor: **ZETACHRON, INC.**
100 North Science Park Road
State College, PA 16803(US)(72) Inventor: **SNIPES, Wallace, C.**
Deepwood Drive
Pine Grove Mills, PA 16868(US)(74) Representative: **van Loon, C.J.J. et al**
Vereenigde Octrooibureaux Nieuwe Parklaan
97
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DescriptionField of the Invention:

5 This invention relates to sustained release compositions for bioactive compounds and more particularly to sustained release oral dosage forms incorporating a drug in an erodible matrix.

Description of the Prior Art:

10 In chemotherapy of diseases it is frequently desirable to maintain the concentration of the therapeutic drug at a relatively constant level in the blood or organ being treated. One method for achieving this goal is to administer the drug continuously at a rate which balances its rate of metabolism and/or excretion. In a hospital environment this goal can be attained by intravenously administering a drug, but outside of such an environment this method of administration is impractical in the great majority of cases. Consequently, the
 15 most common method of administering a drug is orally, in the form of tablets, capsules, and the like, which preferably have sustained release characteristics. The drug released therefrom is usually absorbed from the gastrointestinal tract and reaches the target organ via the blood stream.

Among the various types of sustained release dosage forms which have been developed are erodible matrices, i.e., dosage forms wherein the drug is entrapped in a matrix which upon ingestion gradually
 20 decomposes in the intestinal fluid thereby releasing the drug for absorption. An example of such a dosage form is found in Schmitt, U. S. Patent 4,346,709, wherein the device comprises a drug dispersed in a bioerodible polymer which is a poly(orthoester) or a poly(orthocarbonate) containing an erosion rate modifier. The erosion rate modifiers of Schmitt are mono-and polybasic organic acids which adjust the pH at the surface of the erodible matrix to accelerate or retard the decomposition of the polymer in the gastric
 25 or intestinal environment.

In a further example, Sothmann, et al., in U. S. Patent 4,351,825, disclose a sustained release oral dosage form wherein a drug is dispersed in a matrix of a water-insoluble polymethacrylate, e.g., a copolymer of acrylic and methacrylic acid esters containing quaternary ammonium groups or a copolymer
 30 of methacrylic acid and methyl methacrylate, which has an anionic character. The granules of the matrix material are mixed with the active drug and an erosion rate modifier which is an ester of a long chain fatty acid with glycerine or a long chain alcohol.

Additionally, Kleber, et al., in U. S. Patent 4,333,919, disclose controlled release formulations comprised of a drug mixed with a copolymer of lactic and glycolic acids. The formulations may also contain adjuvants such as glyceryl distearate. The formulations are primarily intended for growth stimulants for ruminants.
 35 Accordingly, they are administered by filling open-ended steel cylinders with the formulations and placing the cylinders in the rumen of the animal. The filled steel cylinders remain in the rumen, and the growth stimulant is gradually released as the matrix is eroded by the rumen fluids.

DE-A-3,217,071 describes a drug for the peroral application having an improved biological availability of active ingredients, which contains as sustained release component a fatty acid having a chain length of 10
 40 to 15 atoms or a derivative thereof. According to the only example the combination of myristic acid, polyethylene glycol 6000, sodium bicarbonate and tartaric acid is used; the return of the release of a drug to baseline levels results in 5-6 hours.

GB-A-967,610 discloses sustained release dosage form mixtures of a medicament with a monoester or diester of a polyethylene glycol.

45 US-A-3,947,573 discloses an ophthalmic solution consisting essentially of an aqueous solution of an ethylene oxide polymer having a molecular weight of at least about 100,000 etc.. The ophthalmic aqueous solution according to US-A-3,947,573 is not a composition, erodable by an aqueous liquid.

DE-A-2,501,805 discloses compositions suitable for controlled release of biologically active compounds, e.g. pesticides, comprising a compound dispersed in a mixture of a polyethylene glycol and a polyvinyl
 50 acetate polymer.

US-A-3,374,146 discloses sustained release dosage forms containing a medicament dissolved or suspended in a waxy material which can be myristic acid and may also contain a polyethylene glycol. The examples of this reference disclose mixtures of a medicament with glyceryl monostearate or with a polyethylene glycol of unspecified molecular weight.

55 EP-A-0,097,507 discloses a dosage form for ruminant animals comprising a pellet of compressed nutrient or other biologically active substance coated with a thin brittle layer of a synthetic resin to control the rate of dissolution of the pellet within the rumen.

DE-C-287,292 discloses a dosage form wherein a medicament is coated with an enteric coating to

prevent dissolution of the dosage form before it has reached the small intestine. This reference merely discloses the conventional method of delaying dissolution of a medicament by the use of a fatty enteric coating.

It seems evident from these disclosures, that the erodible formulations of the prior art have generally required specially prepared polymers, and that the rate of erosion of such polymers cannot always be adjusted to provide for preferential release of the drug in a particular portion of the gastrointestinal tract, e.g., in the stomach or small intestine.

Therefore, a need has continued to exist for an erodible matrix, prepared from readily available materials which are suitable for sustained release pharmaceutical formulations, wherein the rate of erosion can be substantially controlled.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide an oral, sustained release dosage form.

A further object is to provide an oral, sustained release dosage form incorporating an erosion rate modifier substance.

A further object is to provide an oral, sustained release dosage form whose formulation and/or structure can be adjusted to release its medication either in the stomach or the small intestine.

A further object is to provide a sustained release composition containing a bioactive compound which is released by erosion of the matrix in an aqueous liquid environment.

A further object is to provide a liquid-erodible composition wherein the rate of erosion can be adjusted by incorporation of an erosion rate modifier.

A further object is to provide a liquid-erodible composition wherein the rate of erosion can be adjusted to vary with the pH of the surrounding aqueous liquid.

Additional objects will become apparent from the description of the invention which follows.

The objects of the invention are achieved by a composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:

- 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
- 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid, and 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;

under the proviso that the total amount of the compounds equals 100% by weight.

The objects of the invention are further achieved by a composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:

- 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
- 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid; and
- 5 to 60% by weight of starch as a disintegrant;

under the proviso that the total amount of the compounds equals 100% by weight.

The invention further relates to a composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:

- 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
- 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid;
- 5 to 60% by weight of starch as a disintegrant; and
- 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;

under the proviso that the total amount of the compounds equals 100% by weight.

A sustained release dosage form according to the invention comprises a matrix of the erodible composition of the invention having dissolved or dispersed therein a bioactive compound to be released over a period of time.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The property of the composition of this invention which makes it useful in sustained release prepara-

tions of bioactive material is its erodible character. Because it is the surface of an erodible composition which dissolves or decomposes into the surrounding medium and the eroding liquid does not substantially penetrate its structure, it is possible to achieve superior control of the dissolution rate of the solid composition, so that it may be used in a variety of applications.

The erodible matrix of this invention is especially suitable for incorporating a drug to be administered over a period of time via the intestinal absorption route. It is formed from a composition comprising solid polyethylene glycol and an amphiphilic erosion rate modifier, and the kinetics of its drug release are determined by the properties of the matrix and the shape of the dosage form. Accordingly, the rate of release can be controlled by varying the size and shape of the dosage form as well as the proportion and type of the erosion rate modifier.

The solid polyethylene glycol component of the erodible matrix of this invention may be any polyethylene glycol (PEG) having a molecular weight from about 1000 to about 20000. All of the polyethylene glycols in this range are solid materials which are soluble in water and which will slowly dissolve when in contact with an aqueous medium. Mixtures of polyethylene glycols of different molecular weights may also be used. A preferred PEG is that having a molecular weight of about 8000. The PEG component of the erodible matrix may be present in amounts ranging from about 5 % to about 95 % by weight of the erodible matrix, preferably from 40 % to 80 % by weight.

The erosion rate modifier is an insoluble amphiphile, that is, a material whose molecule possesses a hydrophilic portion and a lipophilic portion, usually located at opposite ends of a relatively elongated molecule. The presence of lipophilic portions in the erosion rate modifier slows down the rate at which the matrix is eroded when in contact with an aqueous liquid environment. Therefore, the rate of erosion can be slightly retarded by incorporating relatively small amounts of erosion rate modifier and greatly retarded by incorporating relatively large amounts of erosion rate modifier.

The erosion rate modifier can also be chosen to vary the rate of erosion under varying conditions of pH. For example, if the erosion rate modifier is a long chain fatty acid such as myristic acid, the erosion rate of the matrix will be relatively slow in acid media wherein the carboxyl group of the myristic acid is not ionized and the amphiphilic molecule is accordingly relatively hydrophobic. On the other hand, under basic conditions the carboxyl group is ionized, and therefore hydrophilic, which makes the erosion rate considerably faster. Evidently, a dosage form made from such a formulation releases relatively little of a drug in the acidic environment of the stomach, but subsequently more freely releases the drug in the basic environment of the small intestine. In the event that erosion of the matrix in the stomach is desired, then erosion rate modifiers having basic groups which are ionized under acidic conditions can be incorporated in the matrix composition.

The erosion rate modifier can also be chosen to compensate for the effects of charged forms of the bioactive compound on the erosion rate. When the bioactive compound, e. g., a drug, is present in the matrix of the invention in amounts greater than about 2-3 % by weight of the total composition, the ionic character of the drug can affect the rate of erosion at various pH's of the eroding environment. For, example if the erodible matrix contains a basic drug, which will assume a positive charge in the acidic environment of the stomach, thereby increasing the erosion rate, an acidic erosion rate modifier, e. g., a long chain fatty acid such as myristic acid, may be used as an erosion rate modifier. The acid will remain un-ionized in the acidic environment of the stomach and thereby act to retard the erosion rate and counterbalance the effect of the basic drug.

Use of erosion rate modifiers devoid of ionizable hydrophilic groups, such as long chain aliphatic alcohols, results in an erodible matrix whose rate of erosion is not greatly affected by the pH of the environment.

The erosion rate modifier may be present in the erodible compositions of this invention in amounts of about 95 % to about 5% by weight, preferably from about 60 % to about 20 % by weight.

Suitable erosion rate modifiers include C₁₂-C₂₀ fatty acids, such as lauric acid, myristic acid, palmitic acid, stearic acid, and arachidic acid; C₁₂-C₂₀ alcohols, such as lauryl alcohol, myristyl alcohol, palmityl alcohol, stearyl alcohol and arachidyl alcohol, amphiphilic esters of fatty acids with glycerol, particularly monoesters of C₁₂-C₂₀ fatty acids such as glyceryl monopalmitate, C₁₂-C₂₀ amines such as lauryl amine, myristyl amine, palmityl amine, stearyl amine and arachidyl amine, and amides of C₁₂-C₂₀ fatty acids.

In various dosage forms embodiments of this invention, the rate of drug release can be controlled by varying the shape of the dosage form or by coating the surface of the dosage form. For example, an erodible dosage form of the invention may have a cylindrical shape wherein the height of the cylinder is much greater than the diameter, so that most of the area of the cylinder exposed to the erosive action of the aqueous liquid medium is constituted by the curved peripheral surface of the cylinder. When such a cylinder is immersed in a liquid medium the peripheral surface of the cylinder will be eroded. As the

diameter of the cylinder decreases though its erosion, the area of the peripheral surface exposed to the erosive action of the aqueous liquid environment decreases proportionally. Therefore, the dosage form will erode at a rate which will provide approximately first order drug release kinetics. If a cylindrical dosage form has a relatively small height compared with its diameter, so that most of the exposed area is provided by the bases of the cylinder, the eroding surface area of the dosage form will not change greatly as erosion proceeds. In this case the rate of drug release will be substantially constant, i. e., the drug release kinetics will be approximately zero order.

In another embodiment, the surface of the dosage form can be partially coated with a liquid-impervious coating so that only certain surfaces of the dosage form are exposed to the erosive action of the medium. This method also allows for adjusting the kinetics of drug release. For example, if a cylindrical dosage form is coated on its curved peripheral surface so that only the ends of the cylinder are exposed to the erosive action of the medium, the area of the dosage form exposed to erosive action will not change with time. In this embodiment, therefore, the drug will be released at a constant rate, i. e., the release kinetics will be approximately zero order.

In order to assure that the rate of drug release will actually remain substantially constant for this coated cylindrical dosage form, it is necessary that the coating be non-self-supporting. If the coating is self-supporting it will extend beyond the ends of the cylindrical portion remaining after a portion of the dosage form has been eroded. This extension will interfere with the access of the eroding aqueous liquid medium to the ends of the cylinder and will, accordingly, affect the kinetics. Therefore, the preferred coating for this type of dosage form is a very thin friable material which is not self-supporting. With such a coating, any portion extending beyond the end of the cylinder after the immediately underlying matrix has been eroded will be broken off as the dosage form is subjected to agitation in the gastrointestinal tract, thus keeping the uncoated ends of the cylinder fully exposed to the erosive action of the medium.

In most cases it will be convenient to apply the coating material in the form of a melt which solidifies by cooling on the surface of the dosage form. Preferred coating materials are long chain fatty acids having 12 to 20 carbon atoms. Such acids include lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid. The thickness of the coating will typically be from about 0.02 mm to about 0.5 mm.

Additional ingredients can be incorporated into the erodible composition of this invention to modify and/or control the properties of the composition. For example, in order to improve the compatibility between the polyethylene glycol and the erosion rate modifier and prevent phase separation when the molten composition is cooled, a modified polyethylene glycol wherein the OH groups at one or both ends are esterified with long chain fatty acids may be added to the mixture. Suitable long chain fatty acids are aliphatic fatty acids having from about 12 to about 20 carbon atoms such as those disclosed above. Preferred polyethylene glycols to be used in preparing the esterified PEG compatibility enhancers are those having a molecular weight from about 200 to 10000, preferably from about 200 to about 2000, PEG 400 and PEG 600 are particularly preferred materials for preparing the esterified PEG's. For example, the esterified PEG's may be the monoesters and preferably the lauric or stearic ester. More preferred esters are the diesters, particularly the dilauroyl and distearoyl esters. These modified polyethylene glycols are prepared by conventional esterification procedures well known to those skilled in the art, such as reacting the polyethylene glycol with the acid chloride of the chosen acid. The modified polyethylene glycol may be incorporated into the compositions of this invention in any effective amounts, such as in an amount up to about 10 % by weight, preferably from about 0.1 % to about 10 % by weight, and particularly about 2 % by weight.

Starch may also be added to the erodible mixture of this invention as a disintegrant in order to adjust the erosion rate. The starch tends to enhance the erodible characteristics of the composition by causing the solid material to dissolve from the surface without penetration of the aqueous liquid into the interior of the solid form. Any type of starch may be used, particularly a pharmaceutically acceptable and readily available form of starch, such as cornstarch. Starch may be present in amounts of from about 5 % by weight to about 60 % by weight, preferably from about 10 % by weight to about 50 % by weight, and more preferably from about 20 % by weight to about 40 % by weight.

Molding adjuvants may also be added to the compositions of this invention. It has been found that the addition of a polyethylene oxide (PEO) having a molecular weight (MW) from about 100,000 to about 5×10^6 has beneficial effects on the viscosity and plasticity of the composition. This provides for easier mold filling and release of molded forms from the molds, especially when molded dosage forms of this invention are prepared by injection molding. The PEO may be present in an effective amount up to about 2 % by weight, preferably from about 0.05 % by weight to about 1 % by weight, and most preferably about 0.1 % by weight. It will be appreciated by those skilled in the art that injection molding of compositions containing a relatively large number of ingredients, such as the compositions of this invention, is not common. Hence,

some experimentation may be required to determine the exact amount of molding adjuvant needed for a given composition.

The erodible matrix of this invention is useful wherever controlled release of a material into an aqueous liquid environment is desired. Such an erodible material may be used, for example, without an incorporated drug as a coating for a substance designed for a delayed dissolution after immersion in an aqueous liquid. It may serve a similar function when employed as a plug for a container intended to release a material on a delayed-action basis when immersed or contacted with an aqueous liquid.

The erodible composition of this invention may also contain an ecological agent dispersed therein in order to provide for gradual release of the ecological agent into an aqueous liquid environment. An ecological agent is defined for purposes of this invention as a non-pharmaceutical substance which has a biological effect on plants or animals in the environment. An ecological agent may be a pesticide, such as an insecticide or herbicide, a fertilizer, a pheromone, a plant growth hormone, or the like. When dosage forms made from compositions containing such bioactive ingredients contact an aqueous liquid environment the bioactive materials are gradually released into the environment. Accordingly, the compositions of this invention are useful for releasing such ecological agents into bodies of water or into a land environment where they may release their active agents by contact with rain or standing water, so as to maintain an effective concentration of the agent in the environment for a relatively long period of time.

It is preferred to use the erodible matrix of this invention as a carrier for sustained release pharmaceuticals administered orally to individuals in need of a relatively constant concentration of medication. The drugs may be locally or systemically acting drugs, and may be selected from among any group wherein a steady concentration of the drug in the organism is desired. Accordingly, the drug may be selected from among analgesic, anorexic, antiarthritic, antibacterial, antibiotic, anticonvulsant, anti-depressant, antidiabetic, anti-fungal, antihistaminic, anti-hypertensive, anti-inflammatory, anti-neoplastic, antiparkinsonism, anti-pyretic, anticholinergic, anti-inflammatory, anesthetic, antimicrobial, antiviral, anti-ulcer, bronchodilator, cardiovascular, contraceptive, central nervous system affecting, inotropic, vasodilator, vasoconstrictor, decongestant, diuretic, hypoglycemic, hormone, hypnotic, hematinic, electrolyte supplement, germicidal, muscle relaxant, parasympatholytic, parasympathomimetic, tranquilizer, ophthalmic, psychostimulant, vitamin, and the like drugs. The drugs can be administered in the form of the parent compound as well as in the form of pharmaceutically acceptable salts, and precursors.

Preferred drugs for use in the dosage forms prepared according to the invention include clonidine, theophylline, quinidine, dipyridamole, hydrochlorothiazide, scopolamine, indomethacin, furosemide, potassium chloride and the like.

The drug to be released from the dosage form of the invention may be incorporated into the erodible matrix simply by dissolving it in the molten matrix or mixing it therewith.

The proportions of drug and erodible matrix in the dosage forms of this invention may vary within wide limits. Because some drugs are effective in very small doses and others require relatively large doses for effect, the proportions will vary depending on the amount of drug which must be incorporated into the unit dosage form. Accordingly, the drug may constitute in an effective amount up to about 70 % by weight of the composition. More preferably the drug will constitute from about 0.1 % to about 50 % by weight of the composition, with the balance being the erodible matrix.

The unit dosage forms of the invention can be prepared by conventional procedures such as compression molding, tableting, extrusion, and injection molding. It is preferred that the dosage forms of the invention be non-porous in order that the erosion will proceed from the surface of the dosage form. Such non-porous dosage forms are best prepared by solidification of a molten form of the composition containing all ingredients of the composition, and injection molding is especially useful for that purpose. Indeed, the dosage forms of the invention are especially adapted to production by injection molding because the erodible matrix composition of the invention has a relatively low melting temperature, and hence the injection molding can be carried out at a temperature which is not detrimental to the drug contained in the dosage form.

The preferred dosage forms of the invention have a cylindrical shape with a diameter of about 3 mm to about 8 mm, and preferably about 5 mm. The length of the cylindrical dosage form is typically about 5 mm to about 20 mm, and is preferably about 10 mm. The preferred dosage forms may be coated on their peripheral cylindrical surfaces with a liquid-impervious non-self-supporting coating as discussed above.

The sustained release compositions of this invention are prepared by the following general procedure.

A premeasured amount of a polyethylene glycol is melted in a vessel, e. g., a kettle provided with a steam jacket or a heating mantle and equipped with a stirring mechanism. A temperature of about 85 °C is sufficient to melt any of the polyethylene glycols. The premeasured amount of the insoluble amphiphile is then added either as a molten liquid or as a solid. It is preferred to melt the insoluble amphiphile and add it

slowly to the stirred molten PEG. The long chain fatty amphiphiles useful in the compositions of this invention are generally molten at the temperature of the molten PEG and can be readily mixed with the PEG. The bioactive agent, drug or the like is then added and dissolved in the molten mixture. Other ingredients, such as disintegrants (e. g., starch), molding adjuvants (e. g., polyethylene oxide), and the like are then added and the mixture is thoroughly blended. Dosage forms may then be formed directly from the molten mixture by the procedures outlined above.

The invention will now be further elucidated by the following examples which are included by way of illustration only.

In the examples all percentages and parts are weight unless otherwise specified.

Example 1.

This example illustrates the preparation of dosage forms of the invention containing polyethylene glycols of various molecular weights.

A series of compositions were prepared having the following compositions:

A.	PEG-1000	37.5 %
	Myristic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

B.	PEG-4000	37.5 %
	Myristic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

C.	PEG-8000	37.5 %
	Myristic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

D.	PEG-20,000	37.5 %
	Myristic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

Cylindrical dosage forms were molded from the compositions A - D by pouring the molten compositions into open-ended plastic molds made of polyethylene having a diameter of about 6 mm and allowing the melt to cool to room temperature. The solidified composition was then extruded from the molds and cut into lengths to prepare cylindrical dosage forms. In this way dosage forms having a diameter of about 6 mm and a length of about 14 mm and weighing about 0.44 g each were prepared.

The sustained release properties of the dosage forms were then tested by the following procedure:

Simulated intestinal fluid (SIF) was prepared by the following procedure:

- 1) 6.8 g of monobasic potassium phosphate were dissolved in 250 ml of water.
- 2) 190 ml of 0.2 N NaOH was added with stirring.
- 3) 400 ml of water and 10 ml of pancreatin were added.
- 4) The pH of the solution was adjusted with 0.2 N NaOH to 7.5 ± 0.1 .
- 5) The solution was diluted with water to 1000 ml.

Each of the cylindrical dosage forms was placed in 80 ml of SIF at 37 °C and subjected to gentle agitation. The amount of drug released was monitored by measuring the optical density of the aqueous medium at an absorption peak of indomethacin at intervals using an ultraviolet spectrophotometer. Each of

the dosage forms was found to release the drug gradually over a period of several hours.

Cylindrical dosage forms of the same size and shape as above were prepared from each of the compositions A - D, but these cylinders were coated on their cylindrical surfaces with myristic acid by dipping the cylinders in molten myristic acid, withdrawing the cylinders and allowing the myristic acid coating to cool and harden, and then scraping the coating from the ends of the cylinders. These dosage forms were tested in SIF by the same procedure as the uncoated dosage forms. They also were found to release the drug over a period of several hours with the drug release occurring at an approximately constant rate.

Example 2.

This example illustrates variation of the fatty acid erosion rate modifier.

Several dosage forms were prepared by the procedure of Example 1 having the following compositions:

A.	PEG-8000	37.5 %
	Myristic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

B.	PEG-8000	37.5 %
	Palmitic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

C.	PEG-8000	37.5 %
	Stearic acid	15 %
	Starch	22.5 %
	Indomethacin	25 %

The dosage forms were tested by the procedure of Example 1 and were found to release the drug over a period of several hours at a relatively constant rate.

Example 3.

This example illustrates another composition of the invention incorporating additional ingredients.

A sustained release composition was prepared by the general procedure disclosed above having the following composition:

PEG-8000	27 %
Palmitic acid	13 %
PEG 400 monostearate	10 %
PEO (MW 5×10^6)	0.1 %
Cornstarch	49.8 %
Clonidine HCl	0.1 %

The molten mixture was poured onto a surface and allowed to cool and solidify. The solid material was then granulated and fed into an injection molding machine to form dosage forms according to the invention.

Example 6.

This example illustrates preparation of PEG esters.

PEG-8000 was melted in a vessel equipped with a stirrer and heated to 100° C. An amount of myristyl

chloride equivalent to one half of the terminal hydroxyl groups of the PEG was melted and added dropwise to the molten PEG with continuous stirring. Chloroform was added to the mixture and the solution was filtered through filter paper (Whatman No. 4) and allowed to stand overnight to evaporate the solvent. The remaining solvent was evaporated the next day by heating at 60° C. The material so obtained was a hard waxy solid having a melting point of about 60° C.

Example 7.

This example illustrates the preparation of dosage forms of the invention using various drugs.

Sustained release compositions were prepared by the general procedure disclosed above having the following compositions:

A.	PEG (MW 3,350)	37 %
	Stearyl alcohol	15 %
	Theophylline	50 %

B.	PEG 8000	30 %
	Myristic acid	20 %
	PEG 400 monostearate	10 %
	PEO (MW 5×10^5)	0.1 %
	Corn starch	24.9 %
	Dipyridamole	15 %

C.	PEG-8000	2.8 g
	Myristic acid	1.2 g
	Starch	1.8 g
	Hydrochlorothiazide	50 mg

D.	PEG-8000	1.5 g
	Myristic acid	0.6 g
	Starch	0.9 g
	Furosemide	1.0 g

E.	PEG-8000	5 %
	Myristic acid	10 %
	Starch	15 %
	Flubiprofen	70 %

F.	PEG-1000	0.7 g
	PEG-8000	0.7 g
	PEG-20000	0.7 g
	Myristic acid	1.0 g
	Palmitic acid	1.0 g
	Stearic acid	1.0 g
	Starch	0.9 g
	KCl 6.0 g	

G.	PEG-8000	50 %
	Glyceryl monostearate	5 %
	Starch	20 %
	Dipyridamole	25 %

Example 8.

This example illustrates a dosage form of this invention incorporating a pesticide.

A composition of the invention was prepared by the procedure of Example 1 having the following composition:

PEG-8000	37.5 %
Myristic acid	15.0 %
Starch	22.5 %
Carbofuran	25.0 %

Cylindrical dosage forms (uncoated) were prepared by the procedure of Example 1. These dosage forms were found to erode over a period of about one day in an aqueous environment.

Example 9.

This example illustrates the preparation of a coated dosage form of the invention.

A composition was prepared by the procedure of Example 1 having the following composition:

PEG-3350	27 %
Myristic acid	13 %
PEG-400 distearate	2 %
Potato starch	13 %
Quinidine • 2 H ₂ SO ₄	45 %

After mixing the molten composition was poured onto a surface and allowed to cool and harden. The hardened composition was then granulated and introduced into an extrusion apparatus. A cylindrical stream was extruded from the apparatus and coextruded therewith, so as to form a continuous coating over the extruded cylinder, was a liquid impervious coating having the following composition:

Cetyl alcohol	99 %
Diethyl phthalate	1 %

The extruded cylinder was then cut into dosage forms having a length of about 10 mm and dosage forms were tested as in Example 1 and found to release the drug over a period of time.

Claims

1. A composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:

- 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
- 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid, and 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;

under the proviso that the total amount of the compounds equals 100% by weight.

2. A composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid; and
 - 5 to 60% by weight of starch as a disintegrant;under the proviso that the total amount of the compounds equals 100% by weight.
3. A composition erodible by an aqueous liquid containing a polyethylene glycol and an erosion rate modifier, comprising:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid;
 - 5 to 60% by weight of starch as a disintegrant; and
 - 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;under the proviso that the total amount of the compounds equals 100% by weight.
4. A composition according to any one of claims 1-3 additionally comprising a biologically active compound.
5. A sustained release composition in a suitable dosage form for releasing a biologically active compound into its surrounding environment comprising said biologically active compound dispersed in a matrix containing a polyethylene glycol and an erosion rate modifier which, when contacted with an aqueous liquid, erodes progressively, said matrix comprising a mixture of:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid;
 - 5 to 60% by weight of starch as a disintegrant; and
 - 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;under the proviso that the total amount of the compounds equals 100% by weight.
6. The composition of claim 5 additionally comprising up to about 2% by weight of a molding adjuvant consisting of polyethylene oxide having a molecular weight of 100,000 to 5,000,000.
7. A sustained release composition in a suitable dosage form for releasing a biologically active compound into its surrounding environment comprising a pharmaceutically active compound or non-toxic pharmaceutically acceptable salt of said pharmaceutically active compound dispersed in a matrix containing a polyethylene glycol and an erosion rate modifier which, when contacted with an aqueous liquid, erodes progressively, said matrix comprising a mixture of:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in said aqueous liquid;
 - 5 to 60% by weight of starch as a disintegrant; and
 - 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about 10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid which increases the compatibility of the polyethylene glycol and the erosion rate modifier;under the proviso that the total amount of the compounds equals 100% by weight.
8. The composition of claim 7 wherein said compound is clonidine.
9. The composition of claim 7 wherein said compound is dipyrindamole.
10. The composition of claim 7 wherein said compound is furosemide.

11. The composition of claim 7 wherein said compound is indomethacin.
12. The composition of claim 7 wherein said compound is scopolamine.
- 5 13. The composition of claim 7 wherein said compound is a bronchodilator.
14. The composition of claim 13 wherein said bronchodilator is theophylline.
15. A sustained release composition in a suitable dosage form for releasing an ecologically active
10 compound into its surrounding environment comprising said ecologically active compound dispersed in
a matrix containing a polyethylene glycol and an erosion rate modifier which, when contacted with an
aqueous liquid, erodes progressively, said matrix comprising a mixture of:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is amphiphilic compound insoluble in said
15 aqueous liquid;
 - 5 to 60% by weight of starch as a disintegrant, and
 - 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about
10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid
which increases the compatibility of the polyethylene glycol and the erosion rate modifier;
20 under the proviso that the total amount of the compounds equals 100% by weight.
16. The composition of claim 15 wherein said ecologically active compound is a fertilizer.
17. The composition of claim 15 wherein said ecologically active compound is a pesticide.
- 25 18. The composition of claim 15 wherein said ecologically active compound is an insecticide.
19. The composition of claim 15 wherein said ecologically active compound is a herbicide.
- 30 20. The dosage form of claim 5-19 wherein said dosage form has the shape of a cylinder having a
diameter from 3 to 8 mm and a length from 5 to 20 mm.
21. The dosage form of claim 20 additionally comprising at least a partial coating of a liquid impermeable
non-self-supporting coating.
- 35 22. The dosage form of claim 21 wherein said coating comprises a solid C₁₂ - C₂₀ fatty acid.
23. The dosage form of claim 22 wherein said coating comprises myristic acid and/or palmitic acid.
- 40 24. A method of preparing a dosage form for releasing a biologically active compound into an aqueous liquid
environment using a polyethylene glycol and an erosion rate modifier comprising mixing said biologi-
cally active compound with a molten composition comprising a mixture of:
 - 5 to 95% by weight of a polyethylene glycol having a molecular weight of from 1,000 to 20,000;
 - 95 to 5% by weight of an erosion rate modifier which is an amphiphilic compound insoluble in
45 said aqueous liquid;
 - 5 to 60% by weight of starch as a disintegrant; and
 - 0.1 to 10% by weight of a polyethylene glycol having a molecular weight from about 200 to about
10,000 and having at one or both ends OH groups esterified with a C₁₂ - C₂₀ aliphatic fatty acid
which increases the compatibility of the polyethylene glycol and the erosion rate modifier;
50 under the proviso that the total amount of the compounds equals 100% by weight.
25. The method of claim 24 additionally comprising up to about 2% by weight of a molding adjuvant
consisting of polyethylene oxide having a molecular weight of 100,000 to 5,000,000.
- 55 26. The composition of anyone of the preceding claims, characterized in that the erosion rate modifiers
include C₁₂ - C₂₀ fatty acids, such as lauric acid, myristic acid, palmitic acid, stearic acid and arachidic
acid; C₁₂ - C₂₀ alcohols, such as lauryl alcohol, myristyl alcohol, palmityl alcohol, stearyl alcohol and
arachidyl alcohol, amphiphilic esters of fatty acids with glycerol, particularly monoesters of C₁₂ -C₂₀

fatty acids such as glyceryl monopalmitate, C₁₂ - C₂₀ amines such as lauryl amine, myristyl amine, palmityl amine, stearyl amine and arachidyl amine, and amides of C₁₂ - C₂₀ fatty acids.

Patentansprüche

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1. Eine Zusammensetzung, die durch eine wässrige Flüssigkeit erodierfähig ist und ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält, die folgende Bestandteile umfasst:

10

- 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;

- 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist, und 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht von etwa 200 bis etwa 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;

15

unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.

2. Eine Zusammensetzung, die durch eine wässrige Flüssigkeit erodierfähig ist und ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält, die folgende Bestandteile umfasst:

20

- 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;

- 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist; und

- 5 bis 60 Gew.-% Stärke als Desintegriermittel,

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unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.

3. Eine Zusammensetzung, die durch eine wässrige Flüssigkeit erodierfähig ist und ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält, die folgende Bestandteile umfasst:

30

- 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;

- 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist;

- 5 bis 60 Gew.-% Stärke als Desintegriermittel; und

35

- 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen etwa 200 und etwa 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;

unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.

40

4. Eine Zusammensetzung nach einem der Ansprüche 1-3, die zusätzlich eine biologisch aktive Verbindung enthält.

5. Eine Depot-Zusammensetzung in einer angemessenen Dosierform zur Freigabe einer biologisch aktiven Verbindung in das sie umgebende Milieu, die die besagte biologisch aktive Verbindung umfasst, dispergiert in einer Matrix, die ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält und die nach und nach erodiert, wenn sie in Verbindung mit einer wässrigen Flüssigkeit gebracht wird, wobei die besagte Matrix ein Gemisch umfasst aus:

45

- 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;

50

- 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist;

- 5 bis 60 Gew.-% Stärke als Desintegriermittel;

- 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen etwa 200 und etwa 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;

55

unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.

6. Die Zusammensetzung aus Anspruch 5, die zusätzlich bis zu etwa 2 Gew.-% eines Pressling-Hilfsstoffes umfasst, der aus Polyethylenoxid mit einem Molekulargewicht von 100.000 bis 5.000.000 besteht.
- 5 7. Eine Depot-Zusammensetzung in einer angemessenen Dosierform zur Freigabe einer biologisch aktiven Verbindung in das sie umgebende Milieu, die eine pharmazeutisch aktive Verbindung oder ein nicht toxisches, pharmazeutisch akzeptables Salz der besagten pharmazeutisch aktiven Verbindung umfasst, dispergiert in einer Matrix, die ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält und die nach und nach erodiert, wenn sie in Verbindung mit einer wässrigen
10 Flüssigkeit gebracht wird, wobei die besagte Matrix ein Gemisch umfasst aus:
 - 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;
 - 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist;
 - 15 - 5 bis 60 Gew.-% Stärke als Desintegriermittel; und
 - 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen etwa 200 und etwa 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;
 - 20 unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.
8. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung Clonidin ist.
9. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung Dipyridamol ist.
- 25 10. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung Furosemid ist.
11. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung Indometacin ist.
- 30 12. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung Scopolamin ist.
13. Die Zusammensetzung von Anspruch 7, in der die besagte Verbindung ein Bronchodilatator ist.
14. Die Zusammensetzung von Anspruch 13, in der der besagte Bronchodilatator Theophyllin ist.
- 35 15. Eine Depot-Zusammensetzung in einer angemessenen Dosierform zur Freigabe einer ökologisch aktiven Verbindung in das sie umgebende Milieu, die die besagte ökologisch aktive Verbindung umfasst, dispergiert in einer Matrix, die ein Polyethylenglykol und einen Erosionsgeschwindigkeits-Modifikator enthält und die nach und nach erodiert, wenn sie in Verbindung mit einer wässrigen
40 Flüssigkeit gebracht wird, wobei die besagte Matrix ein Gemisch umfasst aus:
 - 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;
 - 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist;
 - 45 - 5 bis 60 Gew.-% Stärke als Desintegriermittel; und
 - 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen etwa 200 und etwa 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;
 - 50 unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.
16. Die Zusammensetzung von Anspruch 15, in der die besagte ökologisch aktive Verbindung ein Düngemittel ist.
- 55 17. Die Zusammensetzung von Anspruch 15, in der die besagte ökologisch aktive Verbindung ein Pestizid ist.
18. Die Zusammensetzung von Anspruch 15, in der die besagte ökologisch aktive Verbindung ein

Insektizid ist.

19. Die Zusammensetzung von Anspruch 15, in der die besagte ökologisch aktive Verbindung ein Herbizid ist.
20. Die Dosierform von Anspruch 5-19 in der die besagte Dosierform die Form eines Zylinders mit einem Durchmesser von 3 bis 8 mm und einer Länge von 5 bis 20 mm hat.
21. Die Dosierform von Anspruch 20, die zusätzlich mindestens einen Teilüberzug eines flüssigkeitsundurchlässigen, nicht selbsttragenden Überzugs umfasst.
22. Die Dosierform von Anspruch 21, in der der besagte Überzug eine feste C₁₂ - C₂₀ Fettsäure umfasst.
23. Die Dosierform von Anspruch 22, in der der besagte Überzug Myristinsäure und/oder Palmitinsäure umfasst.
24. Ein Verfahren zur Herstellung einer Dosierform für die Freigabe einer biologisch aktiven Verbindung in eine wässrige, flüssige Umgebung unter Verwendung eines Polyethylenglykols und eines Erosionsgeschwindigkeits-Modifikators, wobei das Gemisch die besagte biologisch aktive Verbindung mit einer geschmolzenen Verbindung umfasst, die aus folgendem Gemisch besteht:
 - 5 bis 95 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen 1.000 und 20.000;
 - 95 bis 5 Gew.-% eines Erosionsgeschwindigkeits-Modifikators, der eine in der besagten wässrigen Flüssigkeit unlösliche amphiphile Verbindung ist;
 - 5 bis 60 Gew.-% Stärke als Desintegriermittel; und
 - 0,1 bis 10 Gew.-% eines Polyethylenglykols mit einem Molekulargewicht zwischen etwa 200 und 10.000 und mit OH-Gruppen an einem oder an beiden Enden, verestert mit einer C₁₂ - C₂₀ aliphatischen Fettsäure, was zu einer höheren Kompatibilität des Polyethylenglykols und des Erosionsgeschwindigkeits-Modifikators führt;unter der Bedingung, dass die Gesamtmenge der Verbindungen 100 Gew.-% entspricht.
25. Das Verfahren aus Anspruch 24, das zusätzlich bis zu etwa 2 Gew.-% eines Pressling-Hilfsstoffes umfasst, der aus Polyethylenoxid mit einem Molekulargewicht von 100.000 bis 5.000.000 besteht.
26. Die Verbindung eines der oben genannten Ansprüche, dadurch gekennzeichnet, dass die Erosionsgeschwindigkeits-Modifikatoren C₁₂ - C₂₀ Fettsäuren umfassen, wie Laurinsäure, Myristinsäure, Palmitinsäure, Stearinsäure und Arachinsäure; C₁₂ - C₂₀ Alkohole, wie Laurylalkohol, Myristylalkohol, Palmitylalkohol, Stearylalkohol, amphiphile Ester von Fettsäuren mit Glycerin, insbesondere Monoester von C₁₂ - C₂₀ Fettsäuren wie Glycerinmonopalmitate, C₁₂ - C₂₀ Amine wie Laurylamin, Myristylamin, Palmitylamin, Stearylamin und Archidylamin und Amide von C₁₂ - C₂₀ Fettsäuren.

Revendications

1. Composition qui peut être érodée par un liquide aqueux contenant un polyéthylène-glycol et un modificateur de taux d'érosion, comprenant:
 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble dans le dit liquide aqueux, et 0,1 à 10% poids de polyéthylène-glycol présentant un poids moléculaire d'environ 200 à environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un acide gras aliphatique C₁₂ - C₂₀ qui augmente la compatibilité du polyéthylène-glycol et du modificateur de taux d'érosion;à la condition que la quantité totale du composé soit égale à 100% poids.
2. Composition qui peut être érodée par un liquide aqueux contenant un polyéthylène-glycol et un modificateur de taux d'érosion, comprenant:
 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble

dans le dit liquide aqueux; et

- 5 à 60% poids d'amidon comme désintégrant;

à la condition que la quantité totale du composé soit égale à 100% poids.

- 5 3. Composition qui peut être érodée par un liquide aqueux contenant un polyéthylène-glycol et un modificateur de taux d'érosion, comprenant:
 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble dans le dit liquide aqueux;
 - 10 - 5 à 60% poids d'amidon comme désintégrant; et
 - 0,1 à 10% poids de polyéthylène-glycol présentant un poids moléculaire de environ 200 à environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un acide gras aliphatique C_{12} - C_{20} qui augmente la compatibilité du polyéthylène-glycol et du modificateur du taux d'érosion;
 - 15 à la condition que la quantité totale du composé soit égale à 100% poids.
4. Composition selon l'une quelconque des revendications 1 à 3 comprenant, en plus, un composé biologiquement actif.
- 20 5. Composition d'émission continue sous forme d'un dosage approprié pour l'émission d'un composé biologiquement actif dans son milieu environnant, comprenant le dit composé biologiquement actif dispersé dans une matrice contenant un polyéthylène-glycol et un modificateur de taux d'érosion, laquelle, lorsqu'elle entre en contact avec un liquide aqueux, est progressivement érodée, la dite matrice comprenant un mélange de:
 - 25 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble dans le dit liquide aqueux;
 - 5 à 60% poids d'amidon comme désintégrant; et
 - 30 - 0,1 à 10% poids de polyéthylène-glycol présentant un poids moléculaire de environ 200 à environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un acide gras aliphatique C_{12} - C_{20} qui augmente la compatibilité du polyéthylène-glycol et du modificateur du taux d'érosion;
 - à la condition que la quantité totale du composé soit égale à 100% poids.
- 35 6. Composition selon la revendication 5, comprenant en plus jusqu'à 2% poids d'un adjuvant de moulage sous forme d'un oxyde de polyéthylène présentant un poids moléculaire de 100.000 à 5.000.000.
7. Composition d'émission continue sous forme d'un dosage approprié pour l'émission d'un composé biologiquement actif dans son milieu environnant, comprenant un composé pharmaceutiquement actif ou un sel non toxique pharmaceutiquement acceptable du dit composé pharmaceutiquement actif dispersé dans une matrice contenant un polyéthylène-glycol et un modificateur de taux d'érosion, laquelle, lorsqu'elle entre en contact avec un liquide aqueux, est progressivement érodée, la dite matrice comprenant un mélange de:
 - 40 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 45 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble dans le dit liquide aqueux;
 - 5 à 60% poids d'amidon comme désintégrant; et
 - 0,1 à 10% poids de polyéthylène-glycol présentant un poids moléculaire de environ 200 à environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un
 - 50 acide gras aliphatique C_{12} - C_{20} qui augmente la compatibilité du polyéthylène-glycol et du modificateur du taux d'érosion;
 - à la condition que la quantité totale du composé soit égale à 100% poids.
8. Composition selon la revendication 7, dans laquelle la dite composition est de la clonidine.
- 55 9. Composition selon la revendication 7, dans laquelle la dite composition est de la dipyridamole.
10. Composition selon la revendication 7, dans laquelle la dite composition est du furosémide.

11. Composition selon la revendication 7, dans laquelle la dite composition est de l'indométacine.
12. Composition selon la revendication 7, dans laquelle la dite composition est de la scopolamine.
- 5 13. Composition selon la revendication 7, dans laquelle la dite composition est un bronchodilatateur.
14. Composition selon la revendication 13, dans laquelle le dit bronchodilatateur est de la théophylline.
15. Composition d'émission continue sous forme d'un dosage approprié pour l'émission d'un composé
10 écologiquement actif dans le milieu environnant, comprenant le dit composé écologiquement actif
dispersé dans une matrice contenant un polyéthylène-glycol et un modificateur de taux d'érosion,
laquelle, lorsqu'elle entre en contact avec un liquide aqueux, est progressivement érodée, la dite
matrice comprenant un mélange de:
 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 15 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble
dans le dit liquide aqueux;
 - 5 à 60% poids d'amidon comme désintégrant; et
 - 0,1 à 10% poids de polyéthylène-glycol présentant une poids moléculaire de environ 200 à
20 environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un
acide gras aliphatique C₁₂ - C₂₀ qui augmente la compatibilité du polyéthylène-glycol et du
modificateur du taux d'érosion;à la condition que la quantité totale du composé soit égale à 100% poids.
16. Composition selon la revendication 15, dans laquelle le dit composé écologiquement actif est un
25 engrais.
17. Composition selon la revendication 15, dans laquelle le dit composé écologiquement actif est un
pesticide.
- 30 18. Composition selon la revendication 15, dans laquelle le dit composé écologiquement actif est un
insecticide.
19. Composition selon la revendication 15, dans laquelle le dit composé écologiquement actif est un
herbicide.
- 35 20. Forme de dosage selon les revendications 5 à 19, dans laquelle la dite forme de dosage a la forme
d'un cylindre présentant un diamètre de 3 à 8mm et une longueur de 5 à 20mm.
21. Forme de dosage selon la revendication 20 comprenant en plus au moins un recouvrement partiel en
40 un revêtement non autoporteur imperméable aux liquides.
22. Forme de dosage selon la revendication 21 dans laquelle le dit revêtement comprend un acide gras
C₁₂ - C₂₀ solide.
- 45 23. Forme de dosage selon la revendication 22 dans laquelle le dit revêtement comprend de l'acide
myristique et/ou palmitique.
24. Méthode de préparation d'une forme de dosage pour émission d'un composé biologiquement actif
dans un environnement liquide aqueux, utilisant un polyéthylène-glycol et un modificateur de taux
50 d'érosion comprenant le mélange du dit composé biologiquement actif avec une composition fondue
comprenant un mélange de:
 - 5 à 95% poids de polyéthylène-glycol présentant un poids moléculaire de 1.000 à 20.000;
 - 95 à 5% poids de modificateur de taux d'érosion sous forme d'un composé amphiphile insoluble
dans le dit liquide aqueux;
 - 55 - 5 à 60% poids d'amidon comme désintégrant; et
 - 0,1 à 10% poids de polyéthylène-glycol présentant une poids moléculaire de environ 200 à
environ 10.000 et présentant à l'une ou aux deux extrémités des groupes OH estérifiés avec un
acide gras aliphatique C₁₂ - C₂₀ qui augmente la compatibilité du polyéthylène-glycol et du

modificateur du taux d'érosion;
à la condition que la quantité totale du composé soit égale à 100% poids.

25. Méthode selon la revendication 24 comprenant en plus jusqu'à environ 2% poids d'un adjuvant de moulage composé d'oxyde de polyéthylène présentant un poids moléculaire de 100.000 à 5.000.000.

26. Composition selon l'une quelconque des revendications précédentes, caractérisée en ce que les modificateurs de taux d'érosion comprennent des acides gras C_{12} - C_{20} tels que l'acide laurique, l'acide myristique, l'acide palmitique, l'acide stéarique et l'acide arachidique; des alcools C_{12} - C_{20} tels que l'alcool laurique, l'alcool myristique, l'alcool palmitique, l'alcool stéarique et l'alcool arachidique, des esters amphiphiliques d'acides gras avec du glycérol, particulièrement des mono-esters d'acides gras C_{12} - C_{20} tels que le monopalmitate-glycérol, des amines C_{12} - C_{20} tels que l'amine laurique, l'amine myristique, l'amine palmique, l'amine stéarique et l'amine arachidique, et des amides d'acides gras C_{12} - C_{20} .

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